PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

53

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07C 233/80, 235/40, 317/44, 323/60, A61K 31/167, A61P 29/00

A1

(11) International Publication Number: WO 00/48988

(43) International Publication Date: 24 August 2000 (24.08.00)

(21) International Application Number: PCT/EP00/01168

(22) International Filing Date: 12 February 2000 (12.02.00)

(30) Priority Data:
60/120,498 18 February 1999 (18.02.99) US

(71) Applicant: F. HOFFMANN–LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH–4070 Basle (CH).

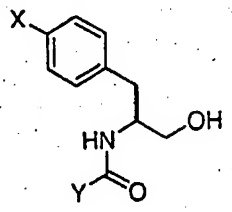
(72) Inventors: SIDDURI, Achytharao; 22 Washington Court, Livingston, NJ 07039 (US). TILLEY, Jefferson, Wright; 19 Evergreen Drive, North Caldwell, NJ 07006 (US).

(74) Agent: LOESCHNER, Thomas; 124 Grenzacherstrasse, CH–4070 Basle (CH).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PHENYLALANINOL DERIVATIVES



(1)

(57) Abstract

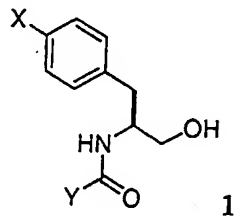
Compounds of formula (1) and the pharmaceutically acceptable salts and esters thereof wherein X and Y are as defined in the specification, are effective inhibitors of the binding of VCAM–1 to VLA–4 *in vivo* and are useful in treating inflammation in inflammatory diseases in which such binding acts to bring on the inflammation.

PHENYLALANINOL DERIVATIVES

Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin (Ig) supergene family, is expressed on activated, but not resting, endothelium. The integrin VLA-4 ($\alpha 4\beta_1$), which is expressed on many cell types including circulating lymphocytes, eosinophils, basophils, and monocytes, but not neutrophils, is the principal receptor for VCAM-1. Antibodies to VCAM-1 or VLA-4 can block the adhesion of these mononuclear leukocytes, as well as melanoma cells, to activated endothelium *in vitro*. Antibodies to either protein have been effective at inhibiting leukocyte infiltration and preventing tissue damage in several animal models of inflammation. Anti-VLA-4 monoclonal antibodies have been shown to block T-cell emigration in adjuvant-induced arthritis, prevent eosinophil accumulation and bronchoconstriction in models of asthma, and reduce paralysis and inhibit monocyte and lymphocyte infiltration in experimental autoimmune encephalitis (EAE). Anti-VCAM-1 monoclonal antibodies have been shown to prolong the survival time of cardiac allografts. Recent studies have demonstrated that anti-VLA-4 mAbs can prevent insulitis and diabetes in non-obese diabetic mice, and significantly attenuate inflammation in the cotton-top tamarin model of colitis.

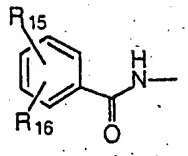
Thus, compounds which inhibit the interaction between α_4-containing integrins, such as VLA-4, and VCAM-1 are useful as therapeutic agents for the treatment of inflammation caused by chronic inflammatory diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS), pulmonary inflammation (e.g., asthma), and inflammatory bowel disease (IBD).

In one aspect the present invention comprises alcohols of the formula:



1

wherein X is a group of the formula X-1



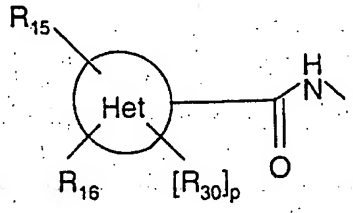
X-1

wherein:

R_{15} is halogen, nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, lower alkoxycarbonyl, carboxy, lower alkyl aminosulfonyl, perfluorolower alkyl, lower alkylthio, hydroxy lower alkyl, alkoxy lower alkyl, alkylthio lower alkyl, alkylsulfinyl lower alkyl, alkylsufonyl lower alkyl, lower alkylsulfinyl, lower alkanoyl, aroyl, aryl, aryloxy;

R_{16} is hydrogen, halogen, nitro, cyano, lower alkyl, OH, perfluorolower alkyl, or lower alkylthio;

or X is a group of the formula X-2



X-2

wherein Het is a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms selected from N,O, and S,

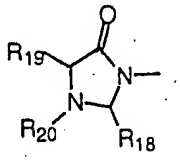
or

Het is a 9- or 10-membered bicyclic heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms selected from O, S, and N;

R_{15} and R_{16} are as in X-1 above, and

R_{30} is hydrogen or lower alkyl, p is an integer from 0 to 1;

or X is a group is of the formula X-3



X-3

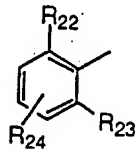
wherein:

R_{18} is aryl, heteroaryl,

R_{19} is substituted or unsubstituted lower alkyl, aryl, heteroaryl, arylalkyl, heteroaryl alkyl, and

R_{20} is substituted or unsubstituted lower alkanoyl or aroyl;

Y is a group of formula Y-1



Y-1

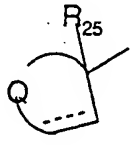
wherein:

R_{22} and R_{23} are independently hydrogen, lower alkyl, lower alkoxy, lower cycloalkyl, aryl, arylalkyl, nitro, cyano, lower alkylthio, lower alkylsulfinyl, lower alkyl sulfonyl, lower alkanoyl, halogen, or perfluorolower alkyl and at least one of R_{22} and R_{23} is other than hydrogen, and

R_{24} is hydrogen, lower alkyl, lower alkoxy, aryl, nitro, cyano, lower alkyl sulfonyl, or halogen;

or Y is a group Y-2 which is a five or six membered heteroaromatic ring bonded via a carbon atom to the amide carbonyl wherein said ring contains one, two or three heteroatoms selected from the group consisting of N, O and S and one or two atoms of said ring are independently substituted by lower alkyl, cycloalkyl, halogen, cyano, perfluoroalkyl, or aryl and at least one of said substituted atom is adjacent to the carbon atom bonded to the amide carbonyl;

or Y is group Y-3 which is a 3-7 membered ring of the formula:



Y-3

wherein:

R_{25} is lower alkyl, unsubstituted or fluorine substituted lower alkenyl, or a group of formula $R_{26}-(CH_2)_e-$,

R_{26} is aryl, heteroaryl, azido, cyano, hydroxy, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkylthio , lower alkyl sulfonyl, lower alkyl sulfinyl, perfluoro lower alkanoyl, nitro, or

R_{26} is a group of formula $-NR_{28}R_{29}$; R_{28} is H or lower alkyl; R_{29} is hydrogen, lower alkyl, lower alkoxycarbonyl, lower alkanoyl, aroyl, perfluoro lower alkanoylamino, lower alkyl sulfonyl, lower alkylaminocarbonyl, arylaminocarbonyl,

or R_{28} and R_{29} taken together form a 4, 5 or 6-membered saturated carbocyclic ring optionally containing one hetero atom selected from O, S, and N; the carbon atoms in the ring being unsubstituted or substituted by lower alkyl or halogen;

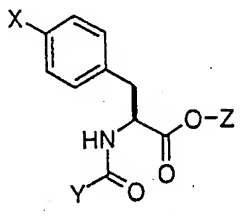
Q is $-(CH_2)_f O-$, $-(CH_2)_f S-$, $-(CH_2)_f N(R_{27})-$, $-(CH_2)_f-$ or a bond;

R_{27} is H, lower alkyl, aryl, lower alkanoyl, aroyl or lower alkoxycarbonyl;

e is an integer from 0 to 4; f is an integer from 1 to 3; and the dotted bond can be optionally hydrogenated.

These compounds are useful as anti inflammatory agents in treating inflammatory diseases These alcohols of Formula 1 are more effective inhibitors of the VCAM-VLA-4 interaction and anti-inflammatory agents *in vivo* than the corresponding acids and esters form which they are derived. They are more bioavailable than these corresponding acids and esters from which are derived. It has been found that the compounds of this invention are more readily orally adsorbed than the acids or esters from which they are derived.

The alcohol compounds of formula I are derived from the corresponding acid and esters of



2

wherein X and Y are as above and Z is lower alkyl or hydrogen.

The preparation of compounds of formula 2 are described in WO 99/10313 and WO 99/10312. The compounds of formula 2 where Y is Y-1 and Y-2 are disclosed in WO 99/10312 as well as their method of preparation. The compounds where Y in formula 2 is Y-3 and their method of preparation are disclosed in WO 99/10313. These alcohols of formula 1 and esters of formula 2 are useful in treating inflammation diseases involving inflammation caused by the binding of VLA-4 to VCAM-1 binding such as rheumatoid arthritis, multiple sclerosis, pulmonary arthritis, asthma and inflammatory bowel diseases. The alcohols of formula 1 are none readily absorbed and more bioavailable than the corresponding carboxylic acids.

As used in this specification, the term "lower alkyl", alone or in combination, means a straight--chain or branched-chain alkyl group containing a maximum of six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.butyl, isobutyl, tert.butyl, n-pentyl, n-hexyl and the like. Lower alkyl groups may be subsituted by one or more groups selected independently from cycloalkyl, nitro, aryloxy, aryl, hydroxy, halogen, cyano, lower alkoxy, lower alkanoyl, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, and substituted amino. Examples of substituted lower alkyl groups include 2-hydroxylethyl, 3-oxobutyl, cyanomethyl, and 2-nitropropyl.

The term "cycloalkyl" means an unsubstituted or substituted 3- to 7-membered carbacyclic ring. Substitutents useful in accordance with the present invention are hydroxy, halogen, cyano, lower alkoxy, lower alkanoyl, lower alkyl, aroyl, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, aryl, heteroaryl and substituted amino.

The term "lower alkoxy" means a straight-chain or branched-chain alkoxy group containing a maximum of six carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy and the like.

The term "lower alkylthio" means a lower alkyl group bonded through a divalent sulfur atom, for example, a methyl mercapto or a isopropyl mercapto group.

The term "aryl" means a mono- or bicylic aromatic group, such as phenyl or naphthyl, which is unsubstituted or substituted by conventional substituent

groups. Preferred subsituents are lower alkyl, lower alkoxy, hydroxy lower alkyl, hydroxy, hydroxyalkoxy, halogen, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, cyano, nitro, perfluoroalkyl, alkanoyl, aroyl, aryl alkynyl, lower alkynyl and lower alkanoylamino. Examples of aryl groups that may be used in accordance with this invention are p-tolyl, p-methoxyphenyl, p-chlorophenyl, m-methylthiophenyl, 2-methyl-5-nitrophenyl, 2,6-dichlorophenyl, 1-naphthyl and the like.

The term "arylalkyl" means a lower alkyl group as hereinbefore defined in which one or more hydrogen atoms is/are replaced by an aryl or heteroaryl group as herein defined. Any conventional arylalkyl may be used in accordance with this invention, such as benzyl and the like.

The term "heteroaryl" means an unsubstituted or substituted 5- or 6-membered monocyclic hetereoaromatic ring or a 9- or 10-membered bicyclic hetereoaromatic ring containing 1, 2, 3 or 4 hetereoatoms which are independently N, S or O. Examples of hetereoaryl rings are pyridine, benzimidazole, indole, imidazole, thiophene, isoquinoline, quinzoline and the like. Substitutents as defined above for "aryl" are included in the definition of heteroaryl.

The term "lower alkoxycarbonyl" means a lower alkoxy group bonded via a carbonyl group. Examples of alkoxycarbonyl groups are ethoxycarbonyl and the like.

The term "lower alkylcarbonyloxy" means lower alkylcarbonyloxy groups bonded via an oxygen atom, for example an acetoxy group.

The term "lower alkanoyl" means lower alkyl groups bonded via a carbonyl group and embraces in the sense of the foregoing definition groups such as acetyl, propionyl and the like.

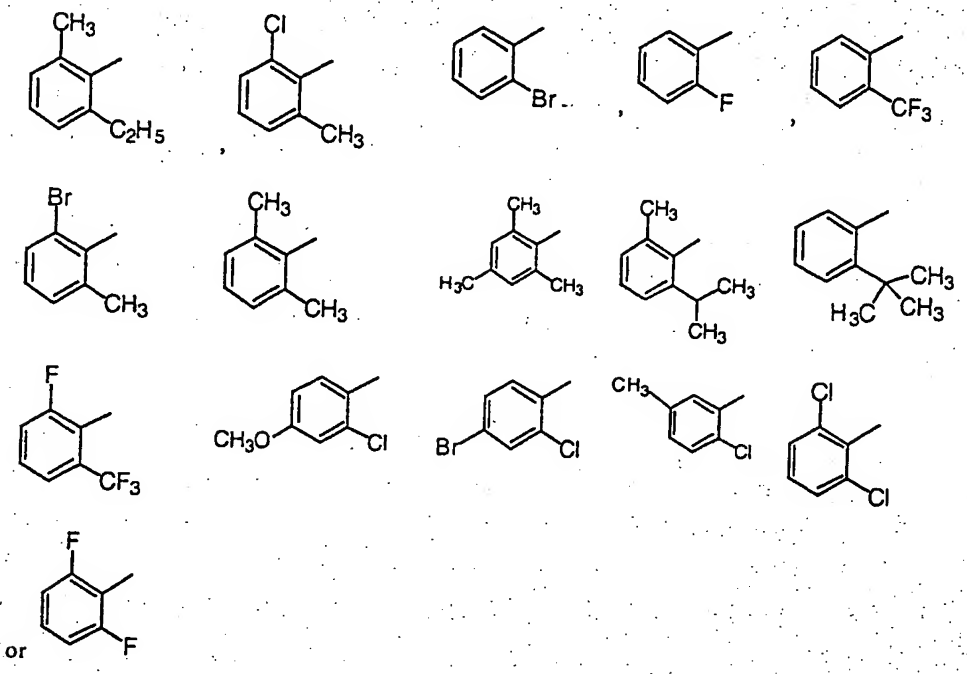
The term "lower alkylcarbonylamino" means lower alkylcarbonyl groups bonded via a nitrogen atom, such as acetylamino.

The term "aroyl" means an mono- or bicyclic aryl or heteroaryl group bonded via a carbonyl group. Examples of aroyl groups are benzoyl, 3-cyanobenzoyl, 2-naphthyl and the like.

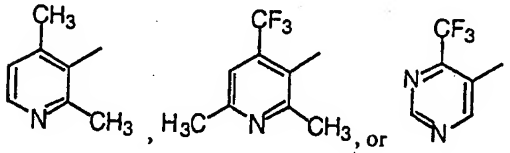
In a particular embodiment of compounds of formula 1 substitutents in Y-1 are preferred wherein R_{22} and R_{23} are lower alkyl, trifluoromethyl, or halogen and

R_{24} is hydrogen, lower alkyl, lower alkoxy, or halogen, particularly wherein R_{22} and R_{23} are preferably lower alkyl or halogen and R24 is preferably hydrogen.

Among the groups Y-1, when R_{23} is lower-alkyl or halogen, Y-1 is preferably:

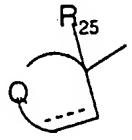


When Y is a group Y-2, the "Het" is preferably a 6 membered monocyclic heteroaromatic ring containing 1, 2 or 3 heteroatoms, particularly wherein the heteroatom is N; more particularly Y-2 is

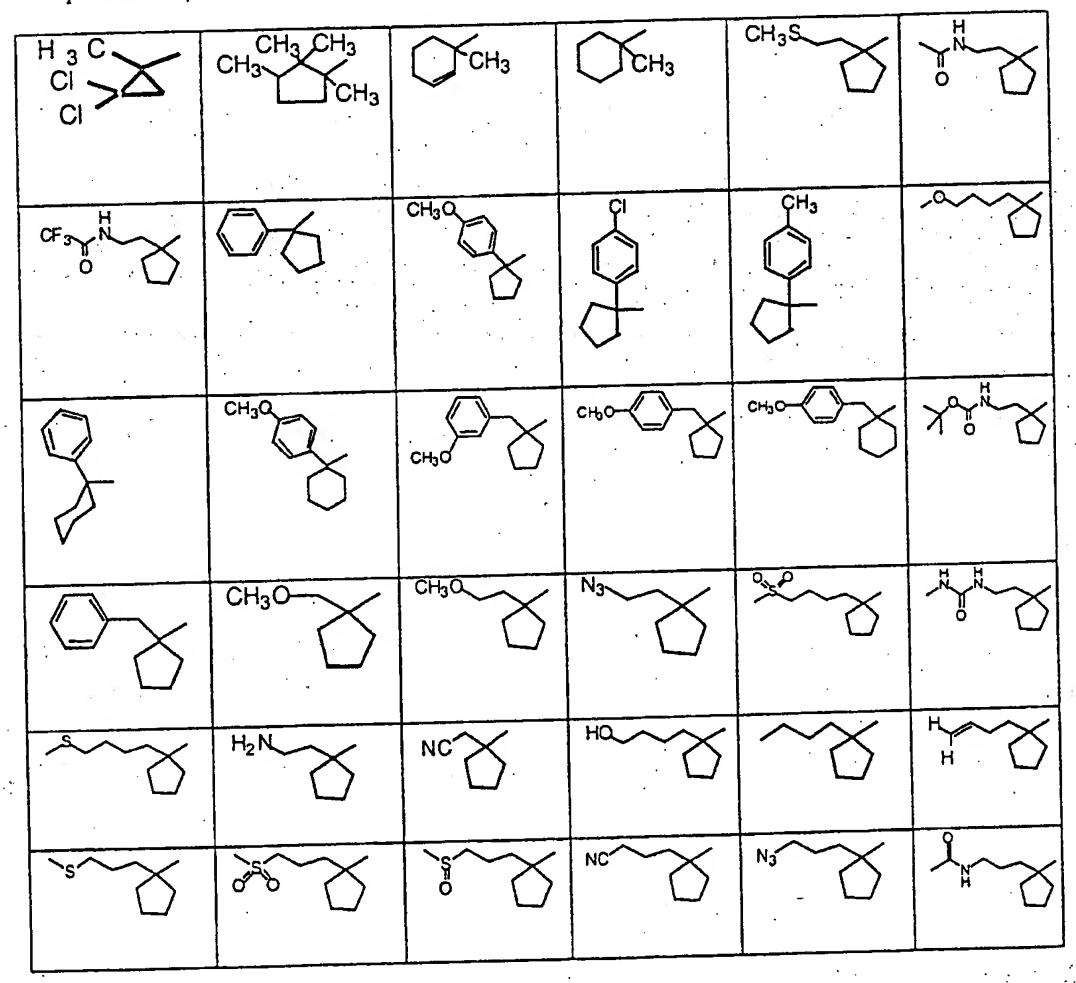


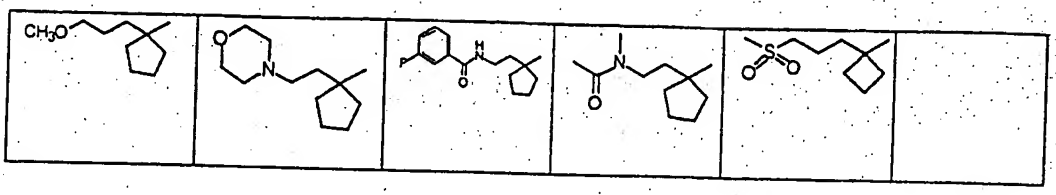
When Y is a group Y-3, Q is preferably -$(CH_2)_f$O-, -$(CH_2)_f$S-, -$(CH_2)_f$N(R_{27})- or -$(CH_2)_f$-, more preferably -(CH2)f-; more particular Y-3 is a four to six membered ring, preferably a cycloalkyl ring, and R_{25} is R_{26}-(CH2)e-; e is 0-4, preferably 2-4, and R_{26} is azido, cyano, hydroxy, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkyl sulfonyl, lower alkyl sulfinyl, perfluoro lower alkanoyl, nitro, lower alkylthio, phenyl or phenyl substituted by alkoxy or halogen, preferably azido, cyano, hydroxy, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkyl sulfonyl, lower alkyl sulfinyl, perfluoro lower alkanoyl,

nitro, lower alkylthio, or R_{26} is NHR_{29} where R_{29} is lower alkanoyl, preferably acetyl, or lower alkylamino carbonyl; Q is $(CH_2)f$ and f is an integer from 1 to 3; and the dotted bond is hydrogenated; more particularly Y-3 is a five or six membered cycloalkyl ring of the formula



with Q being $-(CH_2)f$ and f being 2 and 3; R_{25} being R_{26} $-(CH_2)e-$; e being a integer of 0 to 4, preferably 2 to 4, and R_{26} being lower alkyl, hydroxy, lower alkoxy, lower alkyl thio, or lower alkyl sulfonyl and the dotted bond is hydrogenated; most particularly Y-3 is



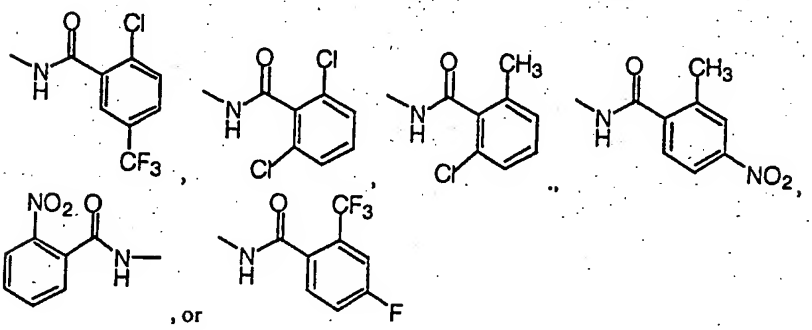


When X is X-1, R_{15} is preferably halogen, nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, perfluorolower alkyl, lower alkylthio, alkylsulfinyl lower alkyl, alkylsufonyl lower alkyl, lower alkylsulfinyl, lower alkanoyl or aroyl and R_{16} is hydrogen, halogen, nitro, cyano, lower alkyl, perfluorolower alkyl, or lower alkylthio.

Within X-1 the group R_{15} is preferably lower alkyl, nitro, halogen (especially chloro or fluoro), perfluoromethyl; or cyano and R_{16} is hydrogen, lower alkyl, nitro, halogen (especially chloro or fluoro), perfluoromethyl, or cyano.

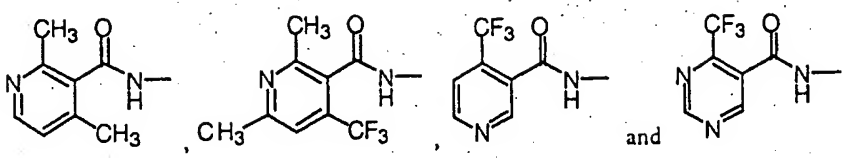
Particularly, R_{15} and R_{16} are independently chloro or fluoro.

The especially preferred groups X-1 are of the formula:



Within X-2 Het is preferably a 5- or 6-membered monocyclic heteroaromatic ring containing 1, 2 or 3 nitrogens, or a nitrogen and a sulfur, or a nitrogen and an oxygen. When Het is a bicyclic heteroaromatic ring, it preferably contains from 1 to 3 nitrogens as the heteroatoms. Where X is X-2, R_{15} is preferably, nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, perfluorolower alkyl, lower alkylthio, lower alkanoyl, or aryl (especially unsubstituted phenyl); R_{16} is preferably hydrogen, halogen, nitro, cyano, lower alkyl, perfluoro lower alkyl; and R_{30}, when present, is preferably hydrogen or lower alkyl.

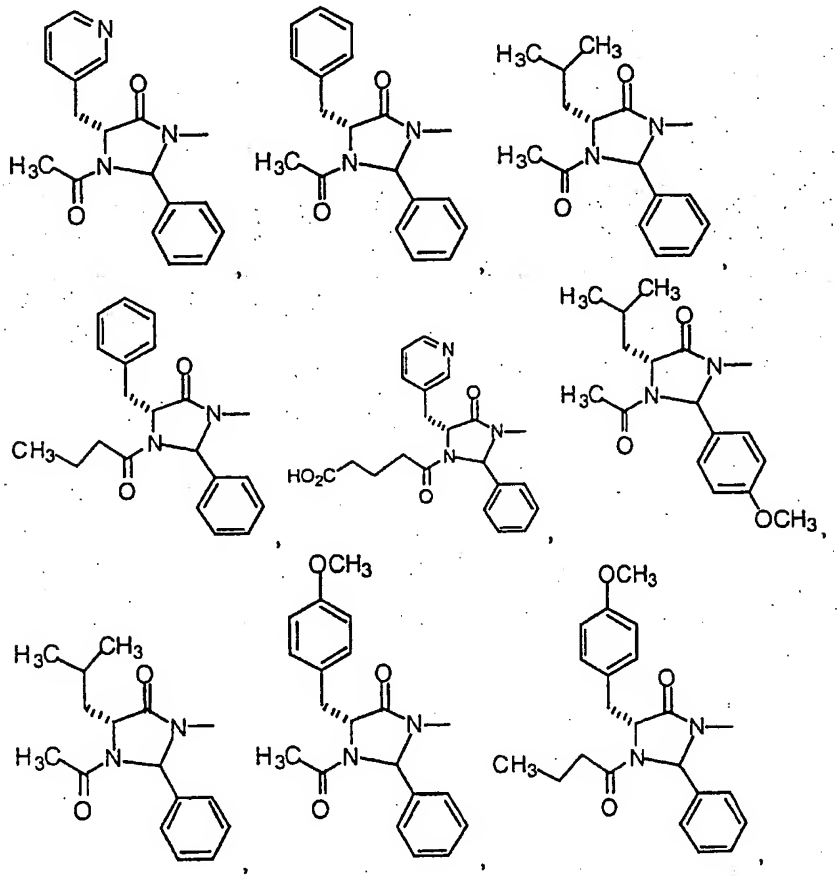
The especially preferred groups X-2 are of the formula:

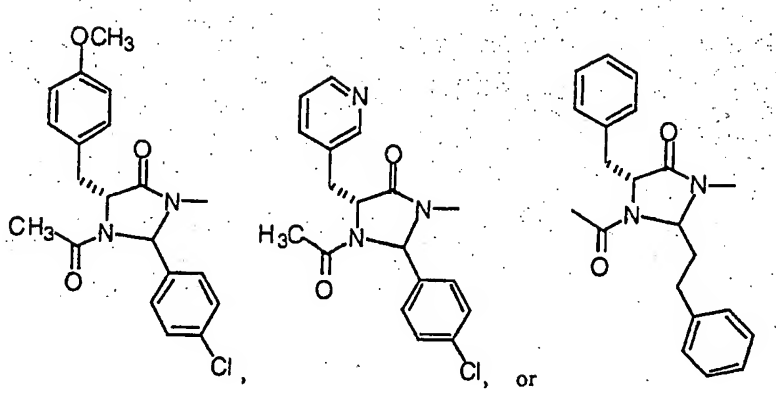


Within the group X-3 R_{18} is preferably phenyl. R_{19} is preferably lower alkyl, which is unsubstituted or substituted by pyridyl or phenyl. R_{20} is preferably lower alkanoyl.

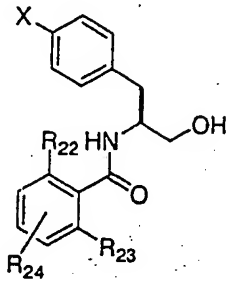
In a further embodiment of X-3 R_{18} is phenyl which is unsubstituted or substituted by halogen or lower alkoxy; R_{19} is phenyl lower alkyl which is unsubstituted or substituted by lower alkoxy, pyridyl lower alkyl, or lower alkyl; and R_{20} is substituted or unsubstituted lower alkanoyl.

The especially preferred groups X-3 are of the formula:





Y is preferably the group Y-1 whereby the invention comprises a compound of the formula:



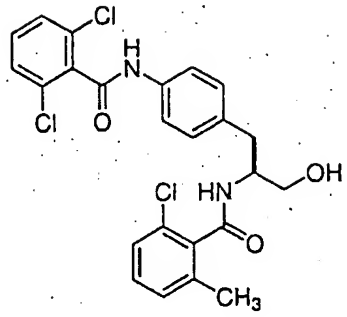
wherein X, R_{22}, R_{23} and R_{24} are as above.

In the group Y-1, R_{22} and R_{23} are preferably lower alkyl or halogen and R_{24} is preferably hydrogen.

The more preferred group X is X-1.

When X is X-1, R_{15} is halogen, nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, perfluorolower alkyl, lower alkylthio, alkylsulfinyl lower alkyl, alkylsufonyl lower alkyl, lower alkylsulfinyl, lower alkanoyl or aroyl and R_{16} is hydrogen, halogen, nitro, cyano, lower alkyl, perfluorolower alkyl, or lower alkylthio.

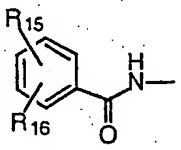
Most preferred is the structure of the formula:



The compounds of the invention can exist as stereoisomers and diastereomers, all of which are encompassed within the scope of the present invention.

The following embodiments describe particular embodiments of the compounds of formula 1 or the present invention.

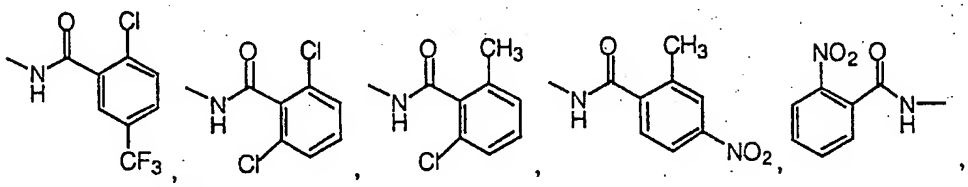
1.1. In one embodiment X is a group of the formula



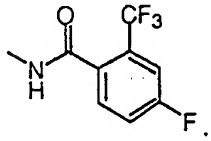
X-1

and R_{15} and R_{16} are as defined above, particularly wherein R_{15} is lower alkyl, nitro, halogen, perfluoromethyl, or cyano, and R_{16} is hydrogen, lower alkyl, nitro, halogen, perfluoromethyl, or cyano; more particularly wherein R_{15} and R_{16} are independently chloro or fluoro.

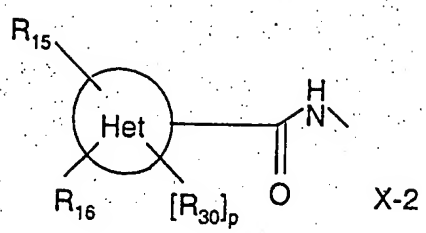
Especially X-1 is selected from the group of



and



1.2. In a further embodiment of a compound of formula 1 X is a group of the formula X-2

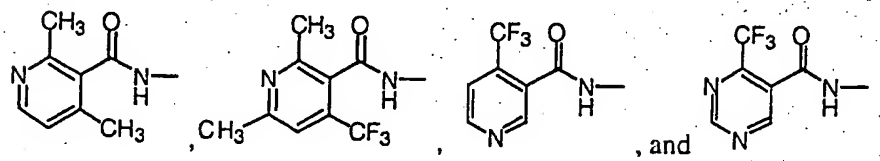


X-2

p, and R_{15}, R_{16}, and R_{30} are as defined above, especially wherein Het is a 5- or 6-memebered monocyclic heteroaromatic ring containing 1, 2 or 3 nitrogens, or a nitrogen and a sulfur, or a nitrogen and an oxygen, or Het is a bicyclic heteroaromatic ring containing from 1 to 3 nitrogens, more particularly Het is a 6 membered monocyclic heteroaromatic ring containing 1 or 2 nitrogens or Het is a 10 membered bicyclic heteroaromatic ring containing one nitrogen, R_{15} is lower alkyl, or perfluoroalkyl, and R_{16} is hydrogen, lower alkyl, or perfluoroalkyl, and R_{30} is absent.

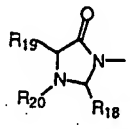
Within X-2 R_{15} is preferably nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, perfluorolower alkyl, lower alkylthio, lower alkanoyl, or aryl (preferably unsubstituted phenyl), especially R_{15} is unsubstituted phenyl. Within X-2 R_{16} is preferably hydrogen, halogen, nitro, cyano, lower alkyl, perfluoro lower alkyl; and R_{30} is hydrogen or lower alkyl.

Especially X-2 is selected from the group of



, and .

1.3. In another embodiment of a compound of formula 1 X is

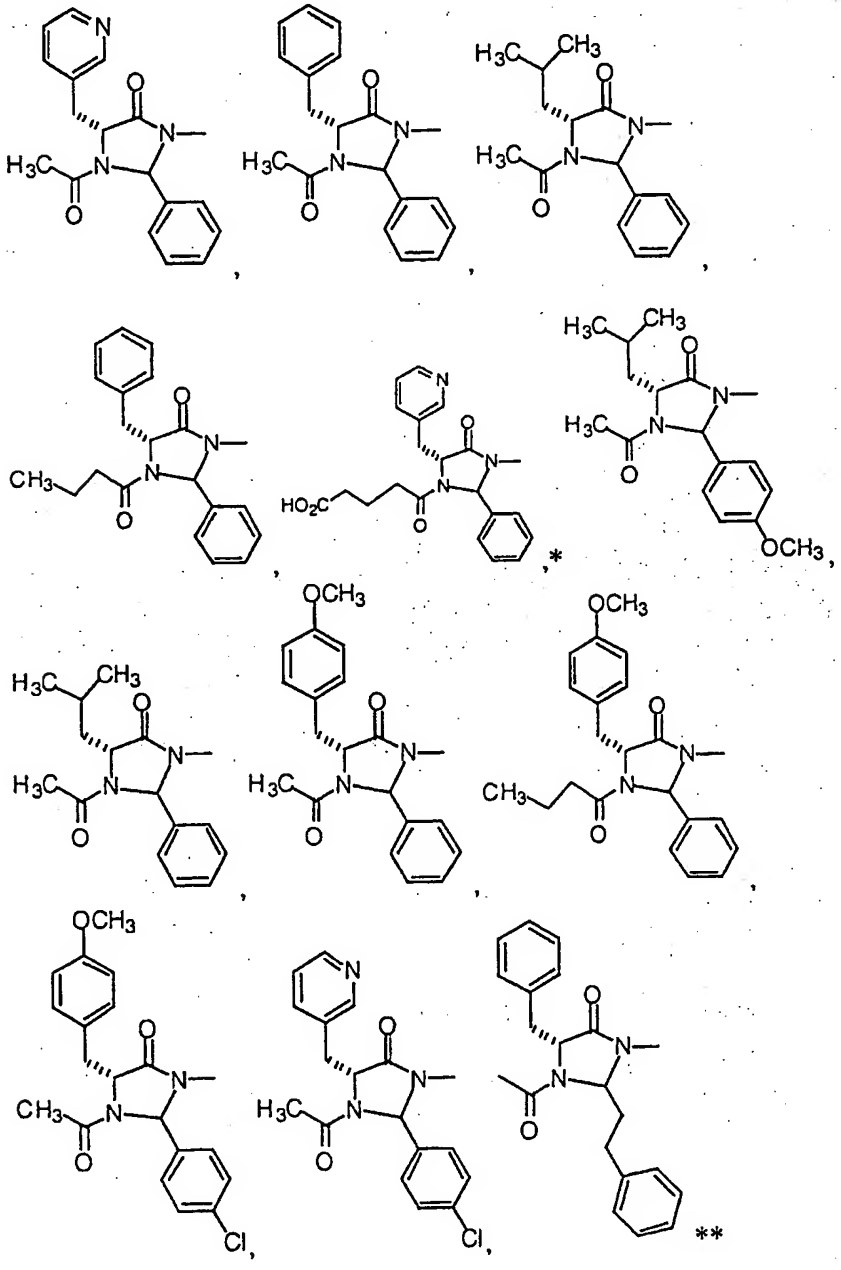


X-3

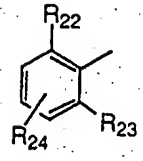
wherein R_{18}, R_{19}, and R_{20} are as defined above, particularly wherein R_{18} is phenyl, and particularly wherein R_{19} is lower alkyl which is unsubstituted or substituted by pyridyl or phenyl, and particularly wherein R_{20} is substituted or unsubstituted lower alkanoyl.

Particular groups of X-3 are preferred wherein R_{18} is phenyl, R_{19} is lower alkyl which is unsubstituted or substituted by pyridyl or phenyl and R_{20} is lower

alkanoyl; or wherein R_{18} is phenyl which is unsubstituted or substituted by halogen or lower alkoxy, R_{19} is phenyl lower alkyl which is unsubstituted or substituted by lower alkoxy, pyridyl lower alkyl, or lower alkyl, and R_{20} is substituted or unsubstituted lower alkanoyl; especially wherein X is selected from the group of

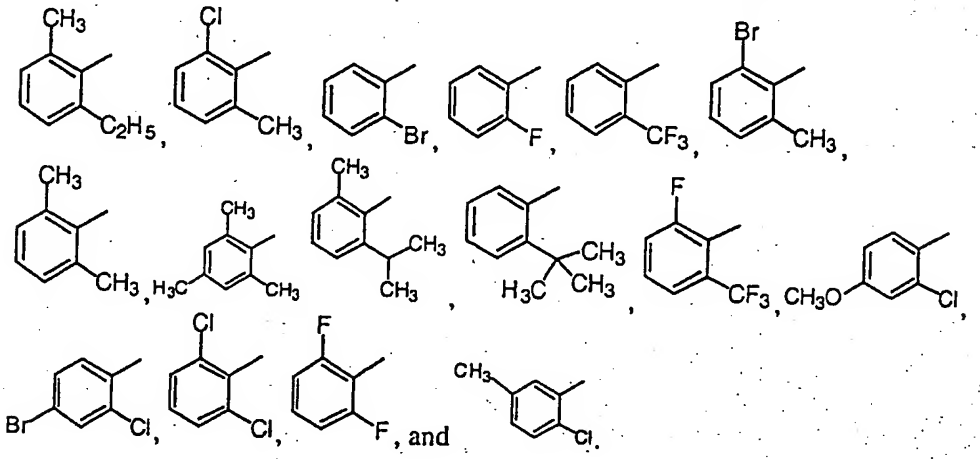


1.4. In a further embodiment of a compound of formula I

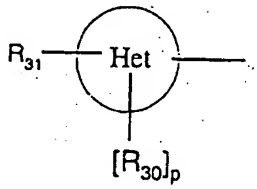


Y-1

wherein R_{22}, R_{23}, and R_{24} are as defined above, especially wherein R_{22} and R_{23} are lower alkyl, trifluoromethyl, or halogen and R_{24} is hydrogen, lower alkyl, lower alkoxy, or halogen, particularly wherein Y-1 is selected from the group of

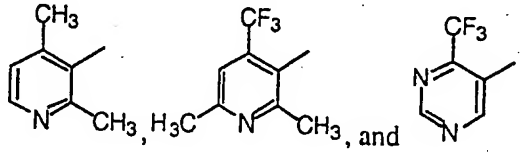


1.5. In a further embodiment of a compound of formula 1 Y is

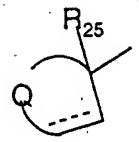


Y-2

wherein p and Het, R_{30} and R_{31}, are as defined above, especially wherein Het is a 6 membered heteroaromatic ring, particularly wherein the heteroatom is N, more particularly wherein Y-2 is selected from the group of

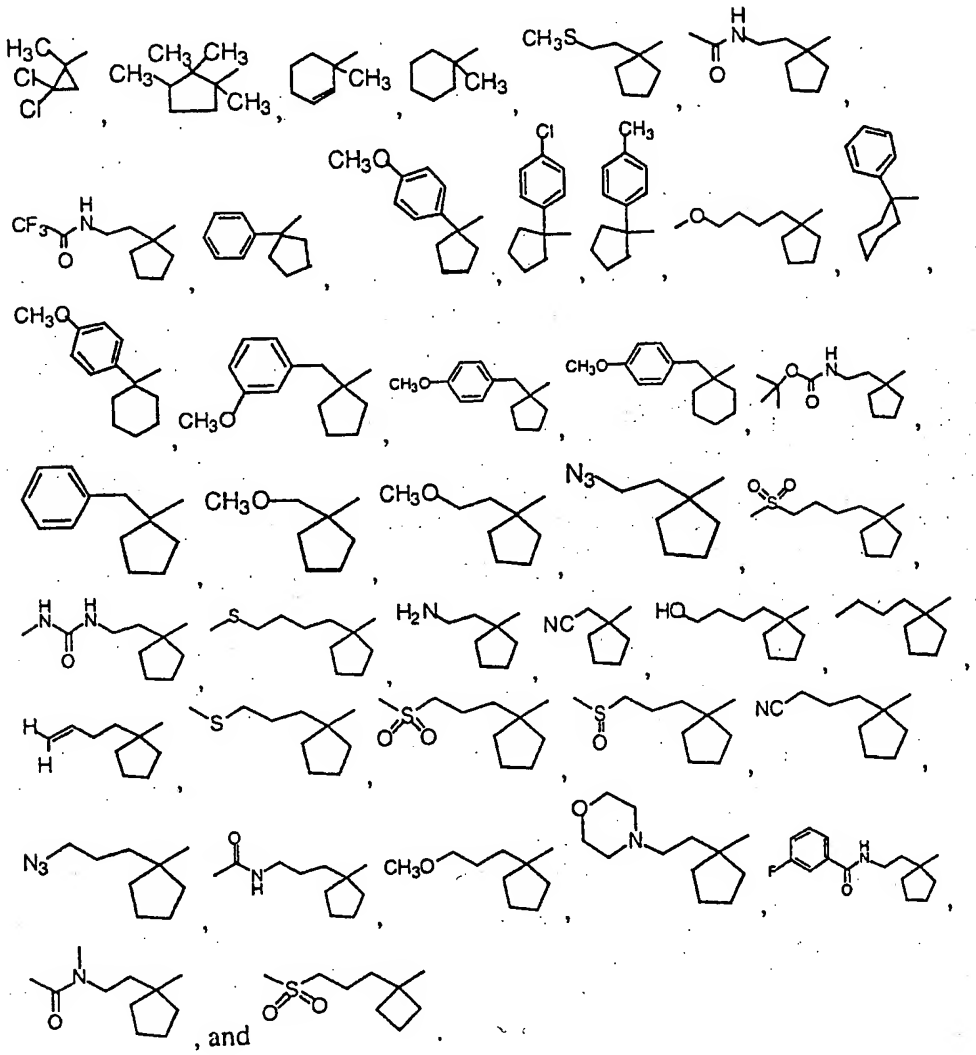


1.6. In yet another embodiment of a compound of formula 1 Y is a group of formula Y-3



Y-3

wherein R_{25} and Q are as defined above; e is an integer from 0 to 4; f is an integer from 1 to 3; and the dotted bond can be optionally hydrogenated, especially wherein Y is selected from the group of the formula:



, and

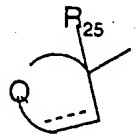
Moreover, it is understood that within the compounds of formula I as defined at the beginning the group X and the group Y can be a group X-1 and Y is a group of formula Y-1, Y-2 or Y-3; or X is X-2 and Y is a group of formula Y-1, Y-2 or Y-3; or X is X-3 and Y is a group of formula Y-1, Y-2 or Y-3, wherein X-1,

X-2, X-3, Y-1, Y-2 and Y-3 are as defined in any of the individual embodiments mentioned above.

More particulary, the following combinations of X and Y are preferred.

In one embodiment X is X-1 and Y is Y-3, more particularly wherein

one of R_{15} and R_{16} is halo, perfluoro lower alkyl, nitro, lower alkyl, and the other is hydrogen halo, perfluoro lower alkyl, nitro, lower alkyl and Y is a five or six membered cycloalkyl ring of the formula



with Q being $-(CH_2)f$ and f being 2 and 3; R_{25} being R_{26} $-(CH_2)e-$; e being a integer of 0 to 4, and R_{26} being lower alkyl, hydroxy, lower alkoxy, lower alkyl thio, or lower sulfonyl and the dotted bond is hydrogenated; with the particular preferred compounds

4-[[(2-methyl-5-nitrophenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)-butyl)cyclopentyl]carbonyl]-L-phenylalanine alcohol,

4-[[(2,6-dimethylphenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)butyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol,

4-[[(2-trifluoromethylphenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)-butyl)cyclopentyl]carbonyl]-L-phenylalanine alcohol,

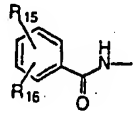
4-[[(2-methyl-5-nitrophenyl)carbonyl]amino]-N-[[1-((4-methylthio)butyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol,

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-((3-methylsulfonyl)-propyl)cyclopenyl]carbonyl]-L-phenylalanin alcohol,

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-(2-methoxyethyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol, or

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-[(4-methylsulfonyl)-butyl]cyclopentyl]-L-phenylalanine alcohol.

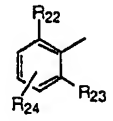
In another preferred combination X is



X-1

R_{16} is hydrogen, lower alkyl, nitro, cyano, halogen, lower alkylthio, perfluoroloweralkyl and R_{15} is lower alkyl, nitro, cyano, halogen, lower alkylsulfonyl, perfluoroloweralkyl, and

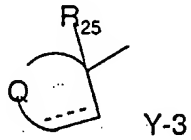
Y is a group of the formula Y-1



Y-1

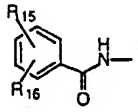
where R_{22} is hydrogen, halogen, trifluoroalkyl, or lower alkyl and R_{23} is halogen , trifluoroalkyl, or lower alkyl, and R_{24} is hydrogen or

Y is a group of the formula Y-3



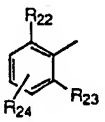
Y-3

which is a four to six membered cycloalkyl ring, R_{25} is R_{26}-(CH_2)e-; e is 2-4 and R_{26} is azido, cyano, hydroxy, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkyl sulfonyl, lower alkyl sulfinyl, perfluoro lower alkanoyl, nitro, or lower alkylthio or R_{25} is NHR_{29} where R_{29} is lower alkanoyl or lower alkylamino carbonyl; Q is (CH_2)f and f is an integer from 1 to 3; and the dotted bond is hydrogenated; particularly X is a group of the formula X-1



X-1

R_{16} is hydrogen, lower alkyl, nitro, cyano, halogen, lower alkylthio, perfluoroloweralkyl and R_{15} is lower alkyl, nitro, cyano, halogen, lower alkylsulfonyl, perfluoroloweralkyl; and Y is



Y-1

where R_{22} is hydrogen, halogen, or lower alkyl and R_{23} is halogen or lower alkyl, and R_{24} is hydrogen, particularly wherein in X-1 R_{15} is halogen and R_{16} is hydrogen

or halogen; R_{22} is hydrogen, halogen, ethyl, or methyl and R_{23} is halogen, ethyl, or methyl.

The compounds and their metabolites of the invention inhibit the binding of VCAM-1 and fibronectin to VLA-4 on circulating lymphocytes, eosinophils, basophils, and monocytes ("VLA-4-expressing cells"). The binding of VCAM-1 and fibronectin to VLA-4 on such cells is known to be implicated in certain disease states, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and particularly in the binding of eosinophils to pulmonary endothelium which is the cause of the pulmonary inflammation which occurs in asthma. Thus, in another aspect the compounds of the present invention would be useful for the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and particularly asthma.

On the basis of their capability to inhibit the binding of VCAM-1 and fibronectin to VLA-4 on circulating lymphocytes, eosinophils, basophils, and monocytes, the compounds and their metabolites of the invention can be used as medicaments for the treatment of disorders which are known to be associated with such binding. Examples of such disorders are rheumatoid arthritis, multiple sclerosis, asthma, and inflammatory bowel disease. The compounds of the invention are preferably used in the treatment of diseases which involve pulmonary inflammation, such as asthma. The pulmonary inflammation which occurs in asthma is related to eosinophil infiltration into the lungs wherein the eosinophils bind to endothelium which has been activated by some asthma-triggering event or substance.

Furthermore, acylphenylalanine derivatives metabolically derived from compounds of the invention also inhibit the binding of VCAM-1 and MadCAM to the cellular receptor alpha4-beta7, also known as LPAM, which is expressed on lymphocytes, eosinophiles and T-cells. While the precise role of alpha4-beta7 interaction with various ligands in inflammatory conditions such as asthma is not completely understood, compounds of the invention which inhibit both alpha4-beta1 and alpha4-beta7 receptor binding are particularly effective in animal models of asthma. Furthermore work with monoclonal antibodies to alpha4-beta7 indicate that compounds which inhibit alpha4-beta7 binding to MadCAM or VCAM are useful for the treatment of inflammatory bowel disease. They would also be useful in the treatment of other diseases in which such binding is implicated as a cause of disease damage or symptoms.

The compounds of the invention can be administered orally, rectally, or parentally, e.g., intravenously, intramuscularly, subcutaneously, intrathecally or transdermally; or sublingually, or as opthalmalogical preparations, or as an aerosol in the case of pulmonary inflammation. Capsules, tablets, suspensions or solutions for oral administration, suppositories, injection solutions, eye drops, salves or spray solutions are examples of administration forms.

Intravenous, intramuscular, oral or inhalation administration is a preferred form of use. The dosages in which the compounds of the invention are administered in effective amounts depending on the nature of the specific active ingredient, the age and the requirements of the patient and the mode of administration. Dosages may be determined by any conventional means, e.g., by dose-limiting clinical trials. Thus, the invention further comprises a method of treating a host suffering from a disease in which VCAM-1 of fibronectin binding to VLA-4-expressing cells is a causative factor in the disease symptoms or damage by administering an amount of a compound of the invention sufficient to inhibit VCAM-1 or fibronectin binding to VLA-4-expressing cells so that said symptoms or said damage is reduced. In general, dosages of about 0.1-100 mg/kg body weight per day are preferred, with dosages of 1-25 mg/kg per day being particularly preferred, and dosages of 1-10 mg/kg body weight per day being especially preferred.

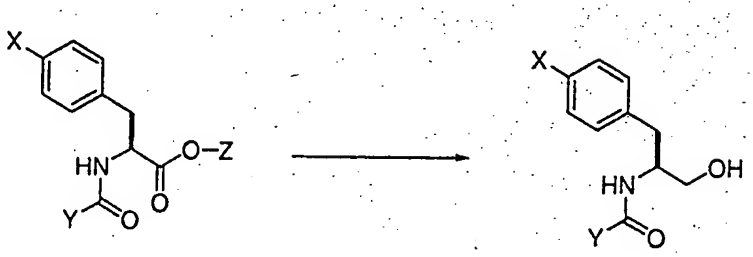
In another aspect, the invention further comprises pharmaceutical compositions which contain a pharmaceutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. Such compositions may be formulated by any conventional means. In this connection the present invention relates to a pharmaceutical preparation, especially a pharmaceutical preparation for the treatment or prophylaxis of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma containing a compound according to any one of the invention or a pharmaceutically acceptable salt or ester thereof together with a compatible pharmaceutical carrier material. Tablets or granulates can contain a series of binders, fillers, carriers or diluents. Liquid compositions can be, for example, in the form of a sterile water-miscible solution. Capsules can contain a filler or thickener in addition to the active ingredient. Furthermore, flavour-improving additives as well as substances usually used as preserving, stabilizing, moisture-retaining and emulsifying agents as well as salts for varying the osmotic pressure, buffers and other additives can also be present.

The previously mentioned carrier materials and diluents can comprise any conventional pharmaceutically acceptable organic or inorganic substances, e.g., water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like.

Oral unit dosage forms, such as tablets and capsules, preferably contain from 25 mg to 1000 mg of a compound of the invention.

In another aspect, the present invention relates to a process for the preparation of compounds of formula 1. The compounds of the present invention may be prepared by any conventional means. In reaction Scheme 1, a compound of formula 2 in which Z is lower alkyl, and which is a known compound prepared as described in WO 99/10313 and WO 99/10312 is treated with a reducing agent capable of selectively reducing a carboxylic ester. For example treatment with a compound of formula 2 with an alkali borohydride, such as sodium borohydride in alcohol solution at about room temperature smoothly effects reduction to give a compound of formula 1.

Scheme 1



wherein X and Y are as above.

General Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer model 241 polarimeter. ^{1}H-NMR spectra were recorded with Varian XL-200 and Unityplus 400 MHz spectrometers, using tetramethylsilane (TMS) as internal standard. Electron impact (EI, 70 ev) and fast atom bombardment (FAB) mass spectra were taken on VG Autospec or VG 70E-HF mass spectrometers. Silica gel used for column chromatography was Mallinkrodt SiliCar 230-400 mesh silica gel for flash chromatography; columns were run under a 0–5 psi head of nitrogen to assist flow. Thin layer chromatograms were run on glass thin layer plates coated with silica gel

as supplied by E. Merck (E. Merck # 1.05719) and were visualized by viewing under 254 nm UV light in a view box, by exposure to I_2 vapor, or by spaying with either phosphomolybdic acid (PMA) in aqueous ethanol, or after exposure to Cl_2, with a 4,4'-tetramethyldiaminodiphenylmethane reagent prepared according to E. Von Arx, M. Faupel and M Brugger, *J. Chromatography*, 1976, *120*, 224–228.

Reversed phase high pressure liquid chromatography (RP-HPLC)was carried out using either a Waters Delta Prep 4000 employing a 3 x 30 cm, Waters Delta Pak 15 μM C-18 column at a flow of 40 mL/min employing a gradient of acetonitrile:water (each containing 0.75% TFA) typically from 5 tp 95% acetonitrile over 35-40 min or a Rainin HPLC employing a 41.4 mm x 30 cm, 8 μM, Dynamax™ C-18 column at a flow of 49 mL/min and a similar gradient of acetonitrile:water as noted above.

Dichloromethane (CH_2Cl_2), 2-propanol, DMF, THF, toluene, hexane, ether, and methanol, were Fisher reagent grade and were used without additional purification except as noted, acetonitrile was Fisher hplc grade and was used as is.

Definitions:

THF is tetrahydrofuran,

DMF is N,N-dimethylformamide,

HOBT is 1-hydroxybenzotriazole,

BOP is [(benzotriazole-1-yl)oxy]tris-(dimethylamino)phosphonium hexafluorophosphate,

HATU is O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HBTU is O-benzotriazole-N,N,N',N',-tetramethyluronium hexafluorophosphate,

DIPEA is diisopropylethylamine,

DMAP is 4-(N,N-dimethylamino)pyridine

DPPA is diphenylphosphoryl azide

DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

NaH is sodium hydride

brine is saturated aqueous sodium chloride solution

TLC is thin layer chromatography

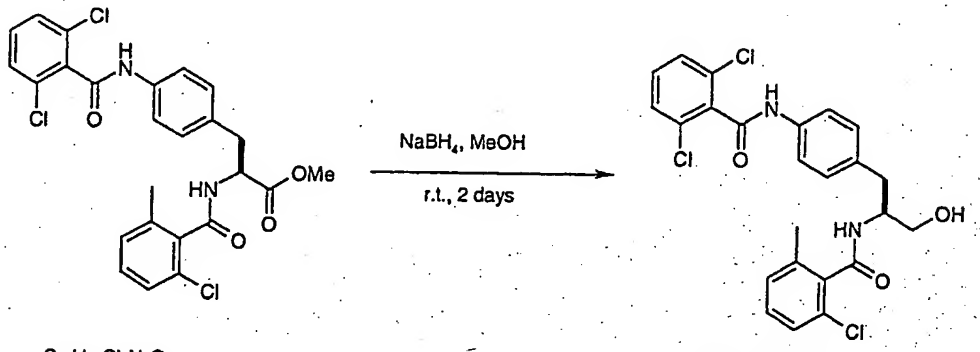
LDA is lithium diisopropylamide

BOP-Cl is bis(2-oxo-3-oxazolidinyl)phosphinic chloride

NMP is N-methyl pyrrolidinone

EXAMPLES

Example 1. Synthesis of 4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[(2-chloro-6-methylphenyl)carbonyl]-L-phenylalaninol.



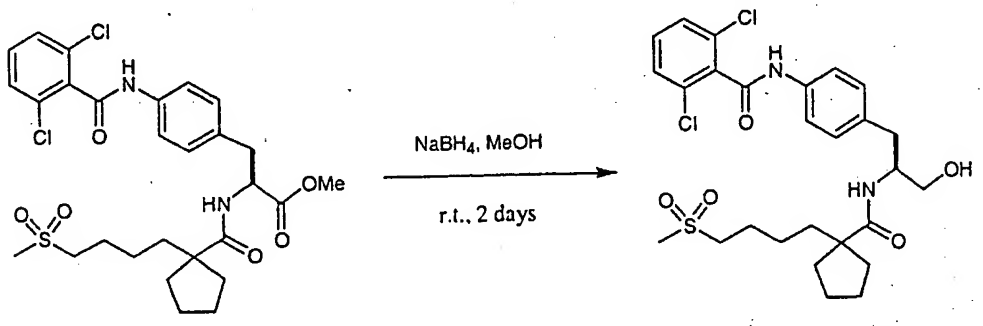
$C_{25}H_{21}Cl_3N_2O_4$
Mol. Wt.: 519.80

$C_{24}H_{21}Cl_3N_2O_3$
Mol. Wt.: 491.79

To a solution of 4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[(2-chloro-6-methylphenyl) carbonyl]-L-phenylalanine methyl ester (9.9 mmol, 5.14 g) in methanol (55 mL) was added excess sodium borohydride (198 mmol, 7.49 g) in six portions during a period of 8 h at room temperature. The slow addition of sodium borohydride is crucial to control an exothermic reaction and evolution of gas with foaming. After addition, the resulting solution was stirred for 2 days at room temperature, at which time the TLC analysis of the mixture indicated the absence of starting material. The excess hydride was destroyed by a slow addition of water (20 mL). The methanol was removed under vacuum and the resulting solid was dissolved in a mixture of water (30 mL), saturated ammonium chloride (80 mL) and ethyl acetate (150 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (70 mL). The combined extracts were washed with brine solution (100 mL) and dried over anhydrous magnesium sulfate. After

filtration of the drying agent, the filtrate was concentrated under vacuum to give 5.3 g of crude compound which was purified by a silica gel column chromatography, eluting with ethyl acetate and hexane (3:1) to afford 4.5 g (92%) of 4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[(2-chloro-6-methylphenyl)-carbonyl]-L-phenylalanine alcohol as a white solid: mp 198-200 °C. HR MS: Obs.mass, 491.0699. Calcd. mass, 491.0696 (M+H).

Example 2. Synthesis of 4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl) butyl)cyclopentyl]carbonyl]-L-phenylalanine alcohol.



$C_{28}H_{34}Cl_2N_2O_6S$
Mol. Wt.: 597.55

$C_{27}H_{34}Cl_2N_2O_5S$
Mol. Wt.: 569.54

To a suspension of 4-[[(2,6-dichlorophenyl)carbonyl]amino]- N-[[1-((4-methylsulfonyl)butyl) cyclopentyl]carbonyl]-L-phenylalanine methyl ester (3.34 mmol, 2.0 g) in methanol (40 mL) was added excess sodium borohydride (10 mmol, 378 mg) in four portions during a period of 6 h at 30-35 °C. The clear solution was stirred for 15 h at room temperature at which time TLC analysis of the mixture indicated the presence of starting material. Then, some more sodium borohydride (16.9 mmol, 640 mg) was added in four portions during a period of 6 h and the solution was stirred for another 3 days. The excess hydride was destroyed by a slow addition of water (10 mL). The methanol was removed under vacuum and the resulting solid was dissolved in a mixture of water (30 mL), saturated ammonium chloride (80 mL), ethyl acetate (100 mL) and tetrahydrofuran (50 mL) at hot condition. The two layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL) and tetrahydrofuran (50 mL). The combined extracts were washed with brine solution (100 mL) and dried over anhydrous magnesium sulfate. After filtration of the drying agent, the filtrate was concentrated under vacuum and crude residue was purified by a silica gel column chromatography eluting with ethyl acetate to afford 0.89 g (47%) of 4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)butyl)cyclopentyl]

carbonyl]-L-phenylalanine alcohol as an amorphous white solid. HR MS: Obs.mass, 569.1645. Calcd. mass, 569.1643 (M+H).

Example 3. Using the general procedure described in example 1, the following compounds can be prepared:

4-[[(2-methyl-5-nitrophenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)butyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol

4-[[(2,6-dimethylphenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)butyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol

4-[[(2-trifluoromethylphenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)-butyl)cyclopentyl]carbonyl]-L-phenylalanine alcohol

4-[[(2-methyl-5-nitrophenyl)carbonyl]amino]-N-[[1-((4-methylthio)butyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-((3-methylsulfonyl)propyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-(2-methoxyethyl)cyclopentyl]-carbonyl]-L-phenylalanine alcohol

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[(2-methyl-6-ethylphenyl)carbonyl]-L-phenylalanine alcohol

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[(2-trifluoromethylphenyl)-carbonyl]-L-phenylalanine alcohol

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[(2-bromophenyl)carbonyl]-L-phenylalanine alcohol

4-[[(2,6-dimethylphenyl)carbonyl]amino]-N-[(2-bromophenyl)carbonyl]-L-phenylalanine alcohol

Example 4. Acute airway inflammation in the atopic primate.

Airway inflammation in the monkey was determined using a modification of the protocol described by Turner et al. (Turner et al., 1994). Adult male cynomolgus monkeys (*Macaca fascicularis*, Hazelton Labs, Denver, PA) weighing between 3.6 - 5.8 kg were used in these studies. All animals exhibited positive skin and airway

responses to *Ascaris suum* antigen and had at least a 3-fold increase in the sensitivity to methacholine (MCh) when subjected to an aerosol of ascaris extract.

On the day of each experiment the animals were anesthetized with ketamine hydrochloride, 12 mg/kg, and xylazine, 0.5 mg/kg, intubated with a cuffed endotracheal tube (3 mm, Mallinckrodt Medical, St. Louis, MO), then seated in an upright position in a specially designed Plexiglass chair (Plas-Labs, Lansing, MI). The endotracheal tube was connected to a heated Fleisch pneumotachograph. Airflow was measured via a Validyn differential pressure transducer (DP 45-24) that was attached to the pneumotachograph. Transpulmonary pressure was measured via a second Validyne transducer (DP 45-24) connected between a sidearm of the tracheal cannula and a 18-gauge intrapleural needle inserted in the intercostal space located below the left nipple. Recordings of pressure and flow and the calculation of R_L were made using the Modular Instruments data acquisition system as described above. Baseline R_L was measured for all animals on the day of each experiment and had an average value of about 0.04 $cmH_20/ml/sec$.

Protocol

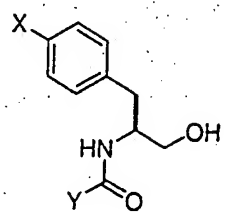
Airway inflammation was induced by exposing the animal to an aerosol of *A. Suum* extract for 60 sec. The aerosol was delivered via a nebulizer (De Vilbiss Model 5000, Healt Care Inc., Somerset, PA) that was attached to the endotracheal tube. The concentration of extract was predetermined for each animal (500 to 50,000 PNU) and caused at least a doubling in the airway resistance. At 24 hour after the antigen challenge, the animals were anesthetized as described previously and placed on a stainless steel table. Airway inflammation was assessed by inserting a pediatric bronchoscope into the airway lumen down to about the 4 or 5^{th} generation bronchi and gently lavaging with 3 X 2 ml aliquots of sterile Hanks Balanced Salt Solution. The recovered lavage fluid then was analyzed for the total cell and differential cell counts using standard hematological techniques.

Drug Treatment

The animals received drug or a vehicle, p.o., administered 2 hours prior to antigen challenge. The compound of example 1 caused a significant decrease in the number and percent of inflammatory cells present in the lavage fluid relative to vehicle treated control animals.

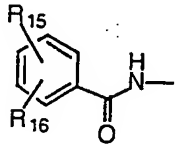
Claims

1. A compound of the formula:



I

wherein X is a group of the formula X-1



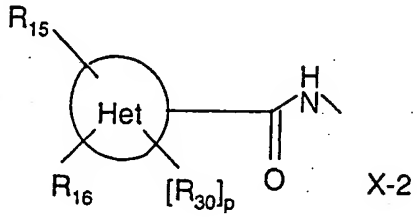
X-1

wherein:

R_{15} is halogen, nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, lower alkoxycarbonyl, carboxy, lower alkyl aminosulfonyl, perfluorolower alkyl, lower alkylthio, hydroxy lower alkyl, alkoxy lower alkyl, alkylthio lower alkyl, alkylsulfinyl lower alkyl, alkylsufonyl lower alkyl, lower alkylsulfinyl, lower alkanoyl, aroyl, aryl, aryloxy;

R_{16} is hydrogen, halogen, nitro, cyano, lower alkyl, OH, perfluorolower alkyl, or lower alkylthio;

or X is a group of the formulaX-2



X-2

wherein Het is a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S,

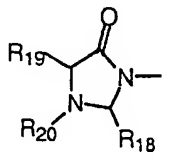
or

Het is a 9- or 10-membered bicyclic heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms selected from O, S, and N;

R_{15} and R_{16} are as in X-1 above, and

R_{30} is hydrogen or lower alkyl, p is an integer from 0 to 1;

or X is a group is of the formula X-3



X-3

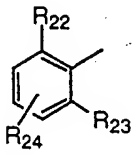
wherein:

R_{18} is aryl, heteroaryl,

R_{19} is substituted or unsubstituted lower alkyl, aryl, heteroaryl, arylalkyl, heteroaryl alkyl, and

R_{20} is substituted or unsubstituted lower alkanoyl or aroyl;

Y is a group of formula Y-1



Y-1

wherein:

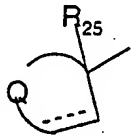
R_{22} and R_{23} are independently hydrogen, lower alkyl, lower alkoxy, lower cycloalkyl, aryl, arylalkyl, nitro, cyano, lower alkylthio, lower alkylsulfinyl, lower alkyl sulfonyl, lower alkanoyl, halogen, or perfluorolower alkyl and at least one of R_{22} and R_{23} is other than hydrogen, and

R_{24} is hydrogen, lower alkyl, lower alkoxy, aryl, nitro, cyano, lower alkyl sulfonyl, or halogen;

or Y is a group Y-2 which is a five or six membered heteroaromatic ring bonded via a carbon atom to the amide carbonyl wherein said ring contains one, two or three heteroatoms selected from the group consisting of N, O and S and one or two

atoms of said ring are independently substituted by lower alkyl, cycloalkyl, halogen, cyano, perfluoroalkyl, or aryl and at least one of said substituted atom is adjacent to the carbon atom bonded to the amide carbonyl;

or Y is group Y-3 which is a 3-7 membered ring of the formula:



Y-3

wherein:

R_{25} is lower alkyl, unsubstituted or fluorine substituted lower alkenyl, or a group of formula $R_{26}—(CH_2)_e-$,

R_{26} is aryl, heteroaryl, azido, cyano, hydroxy, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkylthio , lower alkyl sulfonyl, lower alkyl sulfinyl, perfluoro lower alkanoyl, nitro, or R_{26} is a group of formula $-NR_{28}R_{29}$; R_{28} is H or lower alkyl;

R_{29} is hydrogen, lower alkyl, lower alkoxycarbonyl, lower alkanoyl, aroyl, perfluoro lower alkanoylamino, lower alkyl sulfonyl, lower alkylaminocarbonyl, arylaminocarbonyl,

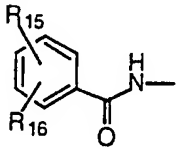
or R_{28} and R_{29} taken together form a 4, 5 or 6-membered saturated carbocyclic ring optionally containing one hetero atom selected from O, S, and N; the carbon atoms in the ring being unsubstituted or substituted by lower alkyl or halogen;

Q is $-(CH_2)_f O-$, $-(CH_2)_f S-$, $-(CH_2)_f N(R_{27})-$, $-(CH_2)_f-$ or a bond;

R_{27} is H, lower alkyl, aryl, lower alkanoyl, aroyl or lower alkoxycarbonyl;

e is an integer from 0 to 4; f is an integer from 1 to 3; and the dotted bond can be optionally hydrogenated.

2. A compound of claim 1 wherein X is a group of the formula



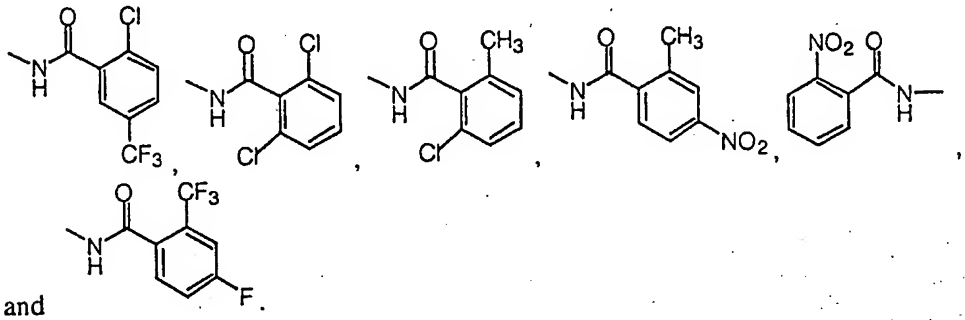
X-1

and R_{15} and R_{16} are as in claim 1.

3. A compound of claim 2 wherein R_{15} is halogen, nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, perfluorolower alkyl, lower alkylthio, alkylsulfinyl lower alkyl, alkylsufonyl lower alkyl, lower alkylsulfinyl, lower alkanoyl or aroyl and R_{16} is hydrogen, halogen, nitro, cyano, lower alkyl, perfluorolower alkyl, or lower alkylthio.

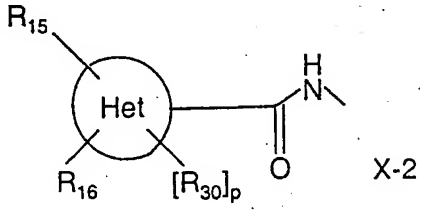
4. A compound of claim 3 wherein R15 and R16 are independently chloro or fluoro.

5. A compound of claim 3 wherein X is selected from the group of



and

6. A compound of claim 1 wherein X is a group of the formula X-2



X-2

wherein p, R_{15}, R_{16}, and R_{30} are as in claim 1.

7. A compound of claim 6 wherein Het is a 5- or 6-membered monocyclic heteroaromatic ring containing 1, 2 or 3 nitrogens, or a nitrogen and a sulfur, or a nitrogen and an oxygen.

8. A compound of claim 6 wherein Het is a bicyclic heteroaromatic ring containing from 1 to 3 nitrogens.

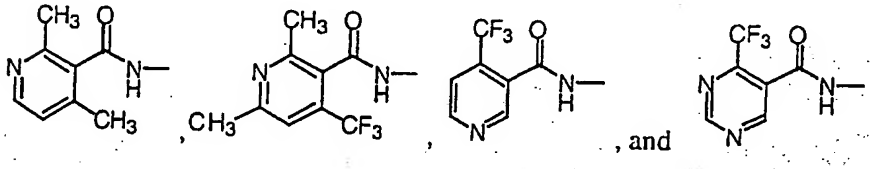
9. A compound of claim 6 wherein R_{15} is nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, perfluorolower alkyl, lower alkylthio, lower alkanoyl, or aryl.

10. A compound of claim 9 wherein R_{15} is unsubstituted phenyl.

11. A compound of claim 6 wherein R_{16} is hydrogen, halogen, nitro, cyano, lower alkyl, perfluoro lower alkyl; and R_{30} is hydrogen or lower alkyl.

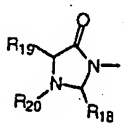
12. A compound of claim 6 wherein Het is a 6 membered monocyclic heteroaromatic ring containing 1 or 2 nitrogens or a 10 membered bicyclic heteroaromatic ring containing one nitrogen, R_{15} and R_{16} are independently hydrogen, lower alkyl, or perfluoroalkyl, and R_{30} is absent.

13. A compound of claim 6 wherein X-2 is selected from the group of



, and .

14. A compound of claim 1 wherein X is



X-3

and R_{18}, R_{19}, and R_{20} are as in claim 1.

15. A compound of claim 14 wherein R_{18} is phenyl.

16. A compound of claim 14 wherein R_{19} is lower alkyl which is unsubstituted or substituted by pyridyl or phenyl.

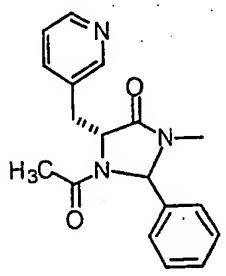
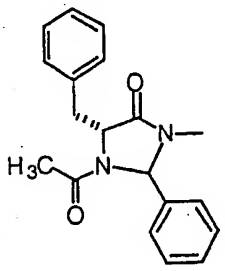
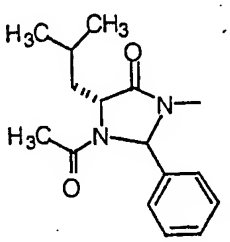
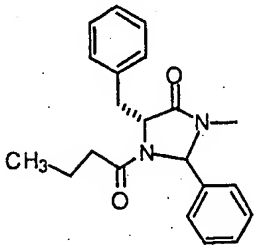
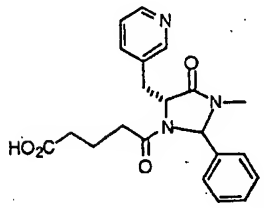
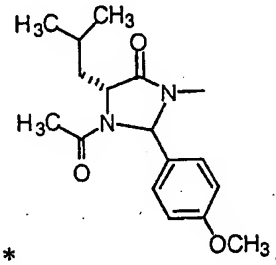
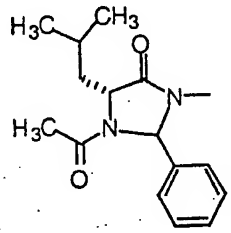
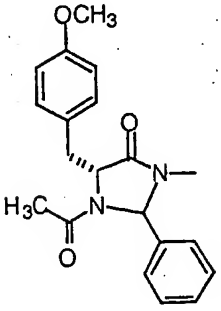
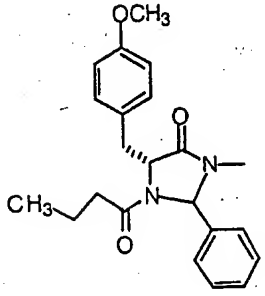
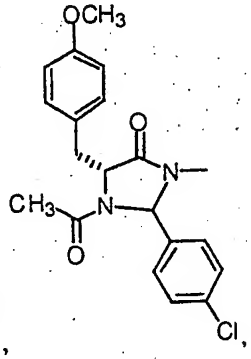
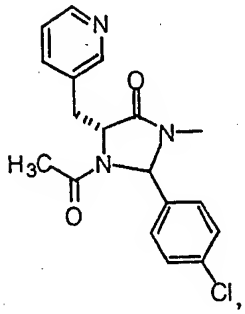
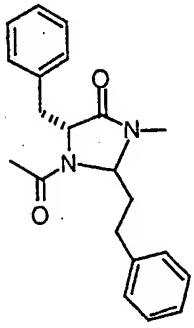
17. A compound of claim 14 wherein R_{20} is substituted or unsubsituted lower alkanoyl.

18. A compound of claim 14 wherein R_{18} is phenyl, R_{19} is lower alkyl which is unsubstituted or substituted by pyridyl or phenyl and R_{20} is lower alkanoyl.

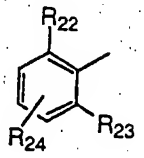
19. A compound of claim 14 wherein R_{18} is phenyl which is unsubstituted or substituted by halogen or lower alkoxy; R_{19} is phenyl lower alkyl which is

unsubstituted or substituted by lower alkoxy, pyridyl lower alkyl, or lower alkyl; and R_{20} is substituted or unsubstituted lower alkanoyl.

20. A compound of claim 14 wherein X is selected from the group of


,

,

,

,

,*

,

,

,

,

,

,

or
.

21. A compound of claim 1 wherein Y is

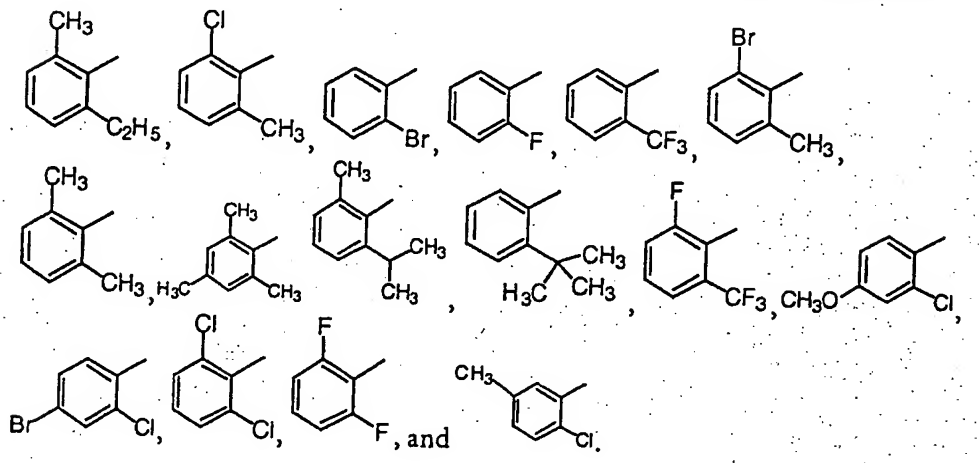


Y-1

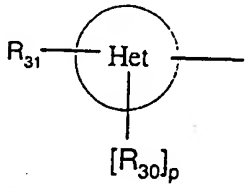
and R_{22}, R_{23}, and R_{24} are as in claim 1.

22. A compound of claim 21 wherein R_{22} and R_{23} are lower alkyl, trifluoromethyl, or halogen and R_{24} is hydrogen, lower alkyl, lower alkoxy, or halogen.

23. A compound of claim 22 wherein Y-1 is selected from the group of



24. A compound of claim 1 wherein Y is



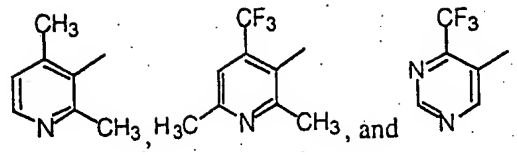
Y-2

and p and Het, R_{30} and R_{31}, are as in claim 1.

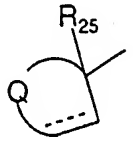
25. A compound of claim 24 wherein Het is a 6 membered monocyclic heteroaromatic ring.

26. A compound of claim 25 wherein the heteroatom is N.

27. A compound of claim 26 wherein Y-2 is selected from the group of



28. A compound of claim 1 wherein Y is a group of formula Y-3

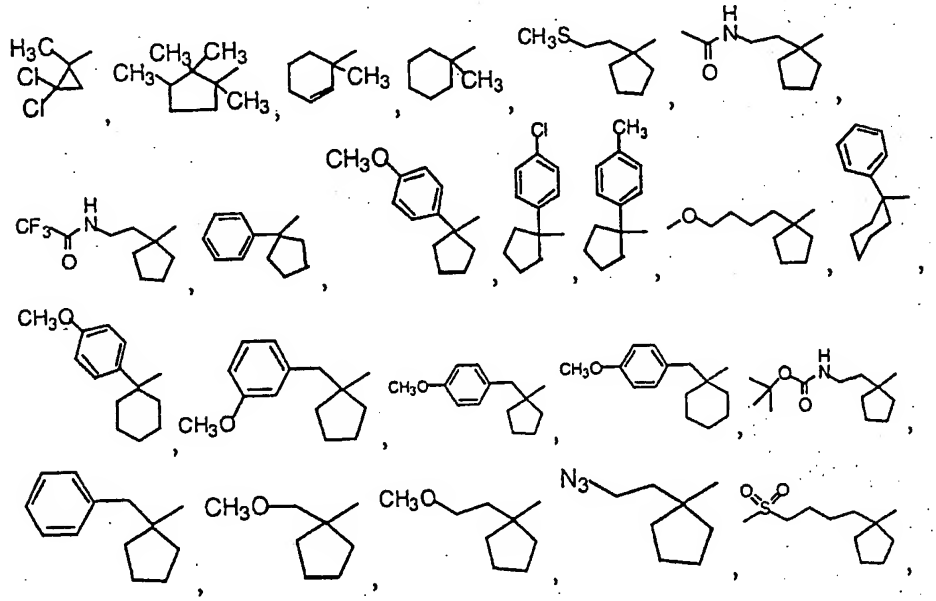


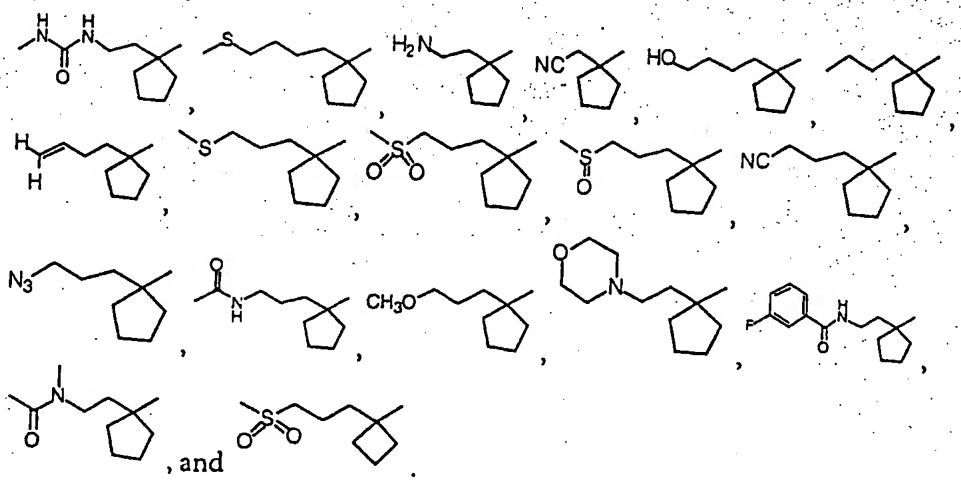
Y-3

and R_{25} and Q are as in claim 1; e is an integer from 0 to 4; f is an integer from 1 to 3; and the dotted bond can be optionally hydrogenated.

29. A compound of claim 28 wherein Y-3 is a four to six membered ring, R_{25} is R_{26}-(CH_2)e-; e is 0-4 and R_{26} is azido, cyano, hydroxy, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkyl sulfonyl, lower alkyl sulfinyl, perfluoro lower alkanoyl, nitro, lower alkylthio, phenyl or phenyl substituted by alkoxy or halogen or R_{26} is NHR_{29} where R_{29} is lower alkanoyl or lower alkylamino carbonyl; Q is (CH_2)f and f is an integer from 1 to 3; and the dotted bond is hydrogenated.

30. A compound of claim 28 wherein Y is selected from the group of the formula:





, and

31. A compound according to claim 1, selected from the group of

4-[[(2,6-dichloro-phenyl)carbonyl]amino]-N-[(2-chloro-6-methylphenyl)-carbonyl]-L-phenylalaninol,

4-[[(2,6-dichloro-phenyl)carbonyl]amino]-N-[(2-bromophenyl)carbonyl]-L-phenylalanine alcohol,

4-[[(2-methyl-5-nitrophenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)-butyl)cyclopentyl]carbonyl]-L-phenylalanine alcohol,

4-[[(2,6-dimethylphenyl)carbonyl]amino]-N-[[1-((4-methylsulfonyl)butyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol,

4-[[(2-trifluoro-methylphenyl) carbonyl]amino]-N-[[1-((4-methylsulfonyl)-butyl)cyclopentyl]carbonyl]-L-phenylalanine alcohol,

4-[[(2-methyl-5-nitrophenyl)carbonyl]amino]-N-[[1-((4-methylthio)butyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol,

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-((3-methylsulfonyl)-propyl)cyclopentyl]carbonyl]-L-phenylalanine alcohol,

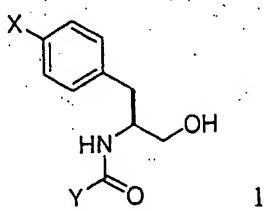
4-[[(2,6-dichlorophenyl) carbonyl]amino]-N-[[1-(2-methoxyethyl)-cyclopentyl]carbonyl]-L-phenylalanine alcohol,

4-[[(2,6-dichlorophenyl)carbonyl]amino]-N-[[1-[(4-methylsulfonyl)-butyl]cyclopentyl]-L-phenylalanine alcohol,

4-[[(2,6-dichloro-phenyl)carbonyl]amino]-N-[(2-bromophenyl)carbonyl]-L-phenylalanine alcohol, or

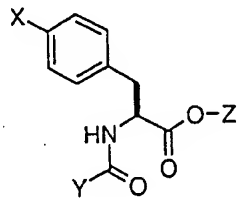
4-[[(2,6-dimethylphenyl)carbonyl]amino]-N-[(2-bromophenyl)carbonyl]-L-phenylalanine alcohol.

32. A process for the preparation of a compound of formula 1



1

wherein X and Y are as defined in claim 1,
characterized in that a compound of formula 2



2

wherein X and Y are as defined above and Z is lower alkyl,
is treated with a reducing agent capable of selectively reducing a carboxylic ester.

33. A compound according to any one of claims 1-31, for use as a medicament, especially in the treatment or prophylaxis of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma.

34. A pharmaceutical preparation, especially a pharmaceutical preparation for the treatment or prophylaxis of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma containing a compound according to any one of claims 1-31 or a pharmaceutically acceptable salt or ester thereof together with a compatible pharmaceutical carrier material.

35. A process for the production of a pharmaceutical preparation, especially a pharmaceutical preparation for the treatment or prophylaxis of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma, which process comprises bringing one or more compounds according to any one of claims 1 to 31 or a pharmaceutically acceptable salt or ester thereof and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with a compatible pharmaceutical carrier.

36. The use of a compound according to any one of claims 1 to 31 or a pharmaceutically acceptable salt or ester thereof in the treatment or prophylaxis if illnesses, especially in the treatment or prophylaxis of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma.

37. The use of a compound according to any one of claims 1 to 31 or a pharmaceutically acceptable salt or ester thereof for the manufacture of a medicament containing as an active substance such aforementioned compound for the treatment or prophylaxis of illnesses, especially for the treatment or prophylaxis of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma.

38. The new compounds, medicaments, processes and uses substantially as hereinbefore described.

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/EP 00/01168

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/80 C07C235/40 C07C317/44 C07C323/60 A61K31/167
A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 53814 A (MERCK) 3 December 1998 (1998-12-03) page 1, line 1 - line 28 page 15, line 11 -page 17, line 6; claims 15-20; examples	1,33-38
A	WO 97 36859 A (G.D.SEARLE) 9 October 1997 (1997-10-09) page 31, line 4 - line 26; claims; examples 47,125,126	1,33-38
P,A	WO 99 10312 A (F. HOFFMANN-LA ROCHE) 4 March 1999 (1999-03-04) claims; examples	1,33-38

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2000	22/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/01168

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 36
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 36 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ,onal Application No
PCT/EP 00/01168

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9853814 A	03-12-1998	NONE	
WO 9736859 A	09-10-1997	AU 2536097 A	22-10-1997
		CA 2250698 A	09-10-1997
		EP 0891325 A	20-01-1999
		US 5952381 A	14-09-1999
WO 9910312 A	04-03-1999	AU 9262098 A	16-03-1999